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09/852,547	05/10/2001	David A. Sirbasku	1944-00800	6474

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EXAMINER
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CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application N .

09/852,547

Applicant(s)

SIRBASKU, DAVID A.

Examiner

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☐ Claim(s) 1-15,17-20 and 66-80 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-15,17-20 and 66-88 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) /
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) Z.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

### DETAILED ACTION

1. Claims 1, 3,-15, 17-19 have been amended. claims 66-80 have been added. Claims 1-15, 17-20 and 66-80 are pending and under consideration. .
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.
3. Lined out references on the enclosed 1449 form, submitted April 11, 2003, indicate that the references were not found with the file. The examiner has accessed the referenced browser-executed addresses. Applicant is invited to provide replacement references. .
4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications 60/203,314 and 60/208,348 upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-15 and 17-20 of this application. Provisional application 60/229,071 was the earliest filed application to contemplate a method wherein an assay of secretory immunoglobulins in a patient would be indicative of an increased susceptibility to steroid hormone responsive cancers. Accordingly, the priority date of the instant application will be the filing date of the '071 provisional application, August 30, 2000.

Applicant argues that claim 1 is fully supported by text from the provisional application 60/208,348, which states "...we conducted studies to demonstrate that IgA in the plasma of female SD-rats is significantly reduced at the time when carcinogenesis is most effective.....These data indicate that rat and human females have the same "window" with regard to IgA". This has been considered but not found persuasive. Instant claim 1 reads "a method to aid in predicting susceptibility of a mammalian subject to development or growth of a steroid hormone responsive cancer in a mucosal epithelial tissue, the method comprising quantitiating and/or detecting an immunoglobulin inhibitor of steroid hormone responsive cells growth in a body fluid or secretion obtained from said subject, wherein said inhibition of steroid hormone responsive cell growth is capable of being reversed by binding of a steroid to a steroid hormone receptor that is active for promoting cell growth, and absence or deficiency of said

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immunoglobulin inhibitor suggesting or indicating that a steroid hormone responsive mucosal epithelial tissue in said subject secretes or is bathed by less than a cell growth inhibitor amount of said immunoglobulin inhibitor". The statement in the provisional application relied upon by applicant, does not provide enablement for the instant claim 1 wherein structure and function of the immunoglobulin inhibitor of steroid hormone responsive cell growth is mediated by the structure and function of the specific steroid hormone receptor that is active for promoting cell growth and wherein binding of a steroid to said receptor reverses the immunoglobulin inhibitor of steroid hormone responsive cell growth. Applicant contends that the immunoglobulin inhibitor is not like the other immunoglobulin inhibitors recognized in the art (see the middle of page 23 of the response). Thus, it is reasonable to assume that the cellular steroid hormone receptor which acts to reverse the inhibition of said immunoglobulin inhibitor also differs from others known in the art. For the reason stated below, the instant specification lacks adequate written description for said immunoglobulin inhibitor of steroid hormone responsive cell growth. The '348 application, also, provides no written description regarding the specific structure or function of the claimed immunoglobulin inhibitor because the steroid hormone receptor that is capable of reversing the action of said immunoglobulin receptor is not described. Therefore, it flows logically, that without a description of the receptor which reverses the inhibiting action of the immunoglobulin inhibitor, the function of said inhibitor which is being reversed by the action of the receptor cannot be qualified. Thus, without the specific disclosure regarding the written description of the inhibitor and the receptor of claim 1, the '348 provisional application fails to support the claimed subject matter.

Section 2163 of the MPEP states

A question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently (see, e.g., *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398), a new or amended claim wherein a claim limitation has been added or removed, or a claim to entitlement of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c). Most typically, the issue will arise in the context of determining whether new or amended claims are supported by the description of the invention in the application as filed (see, e.g., *In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989)), whether a claimed invention is entitled to the benefit of an earlier priority date or effective filing date under 35 U.S.C. 119, 120, or 365(c) (see, e.g., *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 47 USPQ2d 1829 (Fed. Cir. 1998); *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993); *In re Ziegler*, 992 F.2d 1197, 1200, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993)), or whether a specification provides support for a claim corresponding to a count in an interference (see, e.g., *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1971)). Compliance with the written description requirement is a question of fact which must be resolved on a case-by-case basis. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

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and

To comply with the written description requirement of 35 U.S.C. 112, para. 1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation." *Hyatt v. Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998). See also *In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989) (Original specification for method of forming images using photosensitive microcapsules which describes removal of microcapsules from surface and warns that capsules not be disturbed prior to formation of image, unequivocally teaches absence of permanently fixed microcapsules and supports amended language of claims requiring that microcapsules be "not permanently fixed" to underlying surface, and therefore meets description requirement of 35 U.S.C. 112.); *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[W]here no explicit description of a generic invention is to be found in the specification mention of representative compounds may provide an implicit description upon which to base generic claim language."); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) ("To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.") (citations omitted). Furthermore, each claim must include all elements which applicant has described as essential. See, e.g., *Johnson Worldwide Associates Inc. v. Zebco Corp.*, 175 F.3d at 993, 50 USPQ2d at 1613; *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d at 1479, 45 USPQ2d at 1503; *Tronzo v. Biomet*, 156 F.3d at 1159, 47 USPQ2d at 1833. If the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description, or in the case of a claim for priority under 35 U.S.C. 119, 120, or 365(c), the claim for priority must be denied.

The examiner will drawn applicants attention to the above statement that ". Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient". Thus, the mere fact that the observation regarding the female rats may inherently encompass the immunoglobulin inhibitor and the steroid hormone receptor of the instant invention is not a substitute for adequate written description in the '348 application.

5. The rejection of claims 5, 12, and 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record. the rejection of newly added claims 77-79 are also made for reasons of record pertaining to claim 20.

The term "significant increase" and "significant lack of increase" in claim 5 is a relative term which renders the claim indefinite. The term "significant" is not defined by the claim, the

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specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant argues that the term "significant increase" is defined by the specification at paragraph 222. The cited paragraph states:

For the purposes of this Disclosure, the mitogenic response to sex steroid hormones is designated the "steroidogenic effect." For example, the "estrogenic effect" is calculated as the difference between CPD measured in the presence of an estrogen minus CPD in the absence of the steroid. These values equal cell number increases of 2.sup.CPD. The term "androgenic effect" has the same meaning except that it describes growth caused by androgens such as DHT and T. CPD is used herein as a measure of growth because it is a direct calculation of the number of times a cell population undergoes cell division. Furthermore, CPD use permits a direct measure of ED.sub.50 and ED.sub.100 Concentrations in different and in replicate assays. The significance of differences between test dishes and controls was evaluated by the student's t test. Values of  $p < 0.05$  were accepted as significant. Standard deviations ( $\pm$ .SD) are included when appropriate. However, CPD is defined in paragraph 240 as "The cell number results are converted to cell population doublings (CPD) by the following calculation:  $1 \text{ CPD} = \log_{10} \text{ Average Cell Number on Collection Day} - \log_{10} \text{ Average Cell Number on Day Zero}$ "

Thus, the cited text refers specifically to significance in terms of "cell population doublings". Claim 5 refers to a "significant increase in a cell population" which is broader in scope than and increase in cell population doublings. The specification provides no standard for determining the metes and bounds of "significant increase" in a cell population apart from a "significant increase" in cell population doublings.

Claim 12 is rendered indefinite because it does not recite a step linking the method objective to loss or reduction of immunoglobulin inhibition. Claim 12 has been amended to recite the limitation "said detecting comprising testing for loss or reduction of immunoglobulin inhibition of steroid hormone responsive cell growth in said tissue, wherein said inhibition is capable of being reversed by binding a steroid hormone to a cellular steroid hormone receptor that is active for promoting cell growth". However, this limitation does not link the detection with the method objective of aiding in predicting susceptibility of a subject to development of breast cancer.

Claim 20 recites ERg. It is unclear what ERg encompasses, as estrogen-related receptor gamma is abbreviated as ERRg.

Applicant argues that the claims as filed indicates ERgamma rather than ERg. Please note that the examiner does not have easy access to Greek letters in the word processing software. What was clearly pointed out in the rejection was that the Estrogen Related Receptor is conventionally abbreviated as ERR, but the Estrogen Receptor is conventionally abbreviated

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as ER. There are no teachings in the prior art or the specification to indicate the structure or function for an Estrogen Receptor gamma. However, the art recognizes the structure and function of the Estrogen Related Receptor gamma. Thus, it is unclear what is being claimed. In the previous action it was indicated that ERgamma would be read as Estrogen Related Receptor gamma because that it recognized in the art, versus Estrogen Receptor gamma which is not recognized in the art. In the instant response, Applicant concurs with the examiner's interpretation, however, applicant has added dependent claim 79, leading to the interpretation of ERgamma as being an undisclosed form of the estrogen receptor, because tamoxifen is an antagonist of the estrogen receptor, not the estrogen related receptor.

6. Claims 1-15, 17-19, 66-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to written description

The instant claims are method dependent upon the identity of a cellular hormone receptor that is active for promoting cell growth, immunoglobulin inhibitors of steroid hormone responsive cell growth wherein said inhibition is capable of being reversed by binding of steroid hormone to the steroid hormone receptor that is active for promoting cell growth, a poly-Ig receptor that has the property of being able to mediate inhibition by IgA or IgM of steroid hormone responsive cell growth wherein said inhibition is reversible by binding of a steroid hormone to said cellular steroid hormone receptor, allelic imbalance of a poly Ig receptor gene, synthetically altered domains poly Ig receptor that cause loss of ability of said receptor to mediate inhibition of steroid hormone responsive cell growth, genetically defective poly Ig receptors, Fc receptors having the property of being able to mediate inhibition by IgG1 or IgG2 of steroid hormone responsive cell growth, wherein said inhibition is capable of being reversed by the binding of a steroid hormone to a cellular steroid hormone receptor that is active for promoting growth, synthetically altered Fc receptors, defective Fc receptor genes, allelic imbalance in Fc receptor genes and a receptor of unknown structure and function, and

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ERgamma. The specification lacks adequate written description for all of the above. The specification teaches that immunoglobulins bind to poly-Ig receptors or Fc receptors on cells and that this binding causes inhibition of cell growth. This is consistent with teachings in the art as indicated by the art rejections of the previous Office action. However, applicant contends that no protein constituent described by other which inhibits mucosal cell growth possesses the same master switch property as applicants immunoglobulin inhibitors and none are steroid hormone reversible in the same way as Applicants (page 23 of the response, in bold print). However, applicant has not described the structural and functional attributes of the immunoglobulin inhibitors which would render them distinguishable from other immunoglobulins that were not part of the claimed invention. Applicant describes the binding of the immunoglobulin inhibitors to a poly Ig receptor or a Fc receptor. However the binding to said receptors is inherent for any endogenous antibody which would have a Fc region, and is not confined to the specific immunoglobulin inhibitors of the instant invention. Applicant has not identified a steroid hormone receptor that would have signaling properties separate from the well known steroid hormone receptors already recognized in the art. Applicant contends that the examiners interpretation of the abbreviation "ERgamma" is to be interpreted as the Estrogen Related Receptor gamma which is known in the art, however, applicant has added dependent claims wherein tamoxifen is identified as an antagonist of the ERgamma. Tamoxifen is not an antagonist of the Estrogen Related Receptor gamma, and when given the broadest reasonable interpretation in light of newly added claim 79, claims 20 and 77-79 are dependent upon the identity of a steroid hormone receptor that has not been disclosed, as the gamma isoform of the Estrogen Receptor is not recognized in the art or described in the specification. Applicant has not described the functional and structural attributes of a Fc receptor or poly Ig receptor which would define said receptors apart from those known in the art.. Applicant has not taught the structure and function of a steroid or a steroid hormone receptor which would interfere in the inhibition of cell growth from an immunoglobulin inhibitor in a manner that would differ from, for example, the binding of estrogen to the estrogen receptor. Applicant contemplates ERgamma, but has not provided teaching regarding the structure or function of Estrogen Receptor gamma, although Estrogen Related Receptor gamma is known in the art, there is no apparent nexus between the indication of a gamma isoform and structure between two disparate

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receptors. Because applicant contends that the claimed method are novel over the art based the binding of the immunoglobulin inhibit to the poly Ig receptor or the Fc receptor, wherein the inhibition is reversed by the binding of the steroid hormone to the steroid hormone receptor, the claims are given the broadest reasonable interpretation to encompass a genus of immunoglobulin inhibitors, a genus of poly-Ig receptor and Fc receptors, and a genus of steroid hormones and steroid hormone receptors that are not described in the art. Further, method claims 10, 11, 69, and 80 are reliant upon the identity of poly-Ig receptor alleles, poly Ig receptors having altered domains, genetically defective poly Ig receptor genes, alleles of Fc receptor genes and genetically defective Fc receptor genes. The specification provides no teachings regarding DNA sequence or the protein encoded therefrom for any of the aforesaid variants or alleles of the poly Ig receptor or the Fc receptor.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that “[a] written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA” without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

*Id.* At 1568, 43 USPQ2d at 1406. The court concluded that “naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.” *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. “A description of a genus of cDNAs may be achieved by means of a recitation of a

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representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.” Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that “the written description requirement can be met by ‘show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the immunoglobulin inhibitor which demonstrates binding, per Lilly by structurally describing a representative number of immunoglobulin inhibitors that are capable of binding to a specific poly Ig or Fc receptor, and can be reversibly inhibited by binding of a specific steroid hormone to a specific steroid hormone receptor and or by describing “structural features common to the members of the genus, which features constitute a substantial portion of the genus.”. Alternatively, per Enzo, the specification can show that the claimed invention is complete “by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.”

In this case, the specification does not describe the immunoglobulin inhibitor, or the steroid hormone/steroid hormone receptor to practice the methods of the instant invention in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete or partial structure or physical or chemical structure of the immunoglobulin inhibitor

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or steroid hormone receptor, nor any physical or chemical characteristics of the immunoglobulin inhibitors and steroid hormone receptor coupled with a known or disclosed correlation between structure and function. Thus, it is concluded that the specification does not provide a description of the disclosed immunoglobulin inhibitors or steroid/steroid hormone receptor that would satisfy the standard set out in Enzo.

The specification also fails to describe the immunoglobulin inhibitor and steroid hormone/ steroid hormone receptor by the test set out in Lilly. The specification contemplates only a "immunoglobulin inhibitor" and a "steroid hormone/steroid hormone receptor". Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the immunoglobulin inhibitors, poly Ig receptors, Fc receptors, steroid hormone receptors required for the practice of the instant method claims. Since the specification fails to adequately describe disclosed immunoglobulin inhibitor, "a" poly Ig receptor or "a" Fc receptor and steroid hormone/steroid hormone receptor, it also fails to adequately describe the method reliant upon said products.

The disclosure of a immunoglobulin inhibitors and a steroid hormone/ steroid hormone receptor does not describe the claimed genus, because said genus encompasses members with structural and functional attributes which are unknown. Accordingly, one of skill in the art would conclude that applicant was not in possession of the claimed genus.

Regarding alleles and defective gene sequences, the specification does not identify said variant gene sequences. The general knowledge and skill in the art concerning alleles is that the structure of one allele is not representative of other unknown alleles. The same can be said of mutant genes, such as those encoding "defective" poly Ig receptor and defective Fc receptors. thus, the nature of both alleles and defective Fc receptors and defective poly Ig receptors is that they are variant structures and the in the present state of the art, the structure of one does not provide guidance for the structure of other s. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a the known genes encoding the poly Ig receptor and the Fc receptor are

not representative of the variants of the claimed genus. One of skill in the art would conclude that applicant was not in possession of the claimed genus.

(B) As drawn to new matter

Claim 66 embodies the method of claim 5 wherein said significant increase or lack of increase in said cell population is determined using the students t-test and wherein a value of  $p < 0.05$  is significant. The specification does not support this claim limitation, because the specification taught the specific parameters of the T-test only in context of cell population doublings [222]. Claim 5 is broader in scope encompassing changes in cell population which are not confined to cell doublings. Thus, the addition of this limitation represents new matter.

Claim 77 embodies the method of claim 20 comprising increasing the number of B immunocytes in said mucosal epithelial tissues producing IgA or IgM. Claim 78 embodies the method of claim 20 wherein an antagonist of ERgamma is identified. Claim 79 embodies the method of claim 78 wherein said antagonist comprises tamoxifen. It is noted that claims 78-79 are not supported by the originally filed specification. The specification contemplates tamoxifen as a therapeutic, but does not contemplate the identification of tamoxifen in an assay for an antagonists of ERgamma. Further, there is no contemplation of a therapeutic method comprising the increase of B immunocytes in epithelial tissue producing IgA or IgM in the specification.. The specification teaches immunocytes localized in mucosal epithelial tissues but does not contemplate increasing the level of immunocytes in a therapeutic method.

7. Claims 1-7, 9-15, 17-19, 66-76 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claims 1-15, 17-19, 66-80 are drawn to method dependent on the identity of a steroid hormone reversible immunoglobulin inhibitor of steroid hormone responsive cell growth. The art teaches numerous serum factors that cause inhibition of steroid dependent cell growth. For instance, Ghosh et al (Indian Journal of Experimental Biology, Apr 2000, Vol. 38, pp. 313-322, cited in the previous Office action) teach that plasma IgA modulated the growth of Ehrlich ascites cells in vivo. Ehrlich ascites cells respond to estrogen as evidenced by the abstract of Das

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et al (Endocrinologia Japonica, 1976, Vol. 23, pp. 275-279) and are therefore estrogen dependent. Sonnenchein et al (J Steroid Biochemistry, 1996, Vol. 59, pp. 147-154) teach that estrocolyone obtained from serum inhibited estrogen dependent cell growth. Tanji et al (Anticancer Research, Jul-Aug 2000, Vol. 20, pp. 2785-2790, cited in the previous Office action) describe two different proteins that mediated estrogen dependent inhibition of MCF-7 cells. These proteins appear to be normal constituents of serum, therefore it is reasonable to assume they will be detected in normal individuals not suffering from steroid dependent cell growth. The specification provides no guidance on the structure or function of the disclosed immunoglobulin inhibitors which would differentiate them from the prior art immunoglobulin inhibitors. thus, the instant specification doesn't teach one of skill in the art how to make the immunoglobulin inhibitors of the instant invention. Further, the specification does not teach ranges of said inhibitors that would be considered "normal" versus ranges or levels of said inhibitors that would be considered "abnormal" for any of these serum inhibitors. The specification teaches that secretory immunoglobulin binds to steroid responsive epithelial cells and inhibits steroid hormone cell growth. The specification bases the instant claims on the premise that measurement of said secretory immunoglobulins would then be diagnostic for inhibition of steroid responsive cell growth and that decreased levels of said immunoglobulins would then be indicative of decreased inhibition of said cell growth. However, it is known in the art that levels of IgA, the major secretory immunoglobulin, vary as a function of time of day, as well as within a year, and large variations between healthy subjects is documented (Garde et al, Clinical Chemistry, 2000, Vol. 46, pp. 551-559, cited in the previous Office action). The art also teaches that levels of secretory IgA is hormonally regulated in women and thus variable over the course of a menstrual cycle (Gomez et al, Amer J Reproduc Immunol, 1993, Vol. 29, pp. 219-223, cited in the previous Office action). Given that the art teaches that the level of IgA varies with time in a healthy individual and also varies between individual subjects; and given the lack of teaching in the specification regarding ranges or levels of secretory immunoglobulins that were indicative of normal individual or individuals having a steroid hormone responsive disease, one of skill in the art could not use the claimed methods by the detection of the prior art immunoglobulin inhibitors, and further one of skill in the art could not carry out the claimed methods using the immunoglobulin inhibitors disclosed by the instant specification not to be a

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prior art immunoglobulin inhibitor because the specification is not enabling for how to make said inhibitor. The specification is not enabling for how to use said inhibitor either, as it would be necessary to know the structure and function of the steroid hormone receptors by which binding of the steroid hormone induces a reversal of the inhibition of the disclosed immunoglobulin inhibitors. Because one of skill in the art could not use the immunoglobulin inhibitors of the prior art, due to the reasons set forth above, and because the instant specification has not disclosed how to make and use the immunoglobulin inhibitors which are not of the prior art, one of skill in the art would be subject to undue experimentation in order to practice the claimed methods. and the lack of teachings regarding one of skill in the art would not know how to use the claimed methods without undue experimentation.

On the bottom of page 21, applicant submits that claim 7 has been amended to emphasize that the immunoglobulin binding is taking place by a non-antibody-antigen based association. The specification is only enabling for the interaction of the immunoglobulin with the Fc and poly Ig receptors by means of the Fc portion of the antibody, therefore, the amendment has no impact on the scope of the claims. Applicant states that this amendment was made in response to the examiners allegation that when given the broadest reasonable interpretation the claims encompass any IgA, IgM, IgG including non-secretory antibodies. The amendment has not changed this interpretation because all of IgA, IgM and IgG would have an Fc region and thus be capable of binding to the poly Ig receptor or the Fc receptor.

In the middle of page 22, applicant argues that the amendment to claim 12 requiring that inhibition is capable of being reversed by the binding of a steroid hormone to a cellular steroid receptor that is active for promoting cell growth is fully supported by the specification. This has been considered but not found persuasive, as the specification does not teach how to make said inhibitors which differ from endogenous antibodies. The specification requires binding to the poly Ig receptor or binding to the Fc receptor. This is accomplished by any endogenous antibody. The specification fails to teach how to make immunoglobulin inhibitor which would have the characteristics claimed, or conversely, the specification fails to teach a steroid receptor which, when bound by a steroid would reversably inhibit the immunoglobulin inhibitor. Thus, the claims remain rejected under 112, first paragraph.

With regard to the prior art references of Ghosh et al, Das et al, Sonnenschein et al, Tanji et al, applicant contends that the prior art immunoglobulin inhibitors do not possess the same “master switch” property as Applicants immunoglobulin inhibitors and none are steroid hormone reversible in the same way as applicants in that the inhibitory activity is reversible by the growth promoting effect of sufficient hormone via its native cellular receptor (bottom of page 22 to the middle of page 23 of the response). this has been considered but not found persuasive. While the amendment to the claims preclude the rejections over the prior art, the specification is not enabling for how to make the immunoglobulin inhibitor of the instant invention. The specification teaches only the binding of the inhibitor to the poly Ig receptor or the Fc receptor. The prior art immunoglobulin inhibitors also bind to the poly Ig receptor and the Fc receptor, as well as any other endogenous antibody. The specification has no taught how to make and immunoglobulin inhibitor which would have the properties of having the growth inhibitor property reversed by the binding of a steroid hormone to a steroid hormone receptor, nor has the specification taught a specific steroid hormone or a specific steroid hormone receptor which is novel over the art recognized steroid and steroid hormone receptors, or a poly Ig receptor or a Fc receptor which is novel over the prior art. Thus, one of skill in the art could not make the immunoglobulin inhibitors, because the specification provides not guidance as to the structure of said inhibitors and how they would differ from the inhibitors known in the art, and further, the specification does not teach a specific steroid hormone and steroid hormone receptor which would be responsible for the inhibition of the immunoglobulin inhibitor, or convrsely a poly-Ig receptor or a Fc receptor which would confer the property of becomeing inhibited by the binding of a steroid hormone to a steroid hormone receptor.

Applicant argues on pages 23-24 that the immunoglobulin inhibitors of Tanji et al are excluded from the amended claims which recite the limitation of “wherein the inhibition is capable of being reversed by binding to a steroid hormone receptor that is active for promoting growth. This has been considered but not found persuasive. Tanji et al was used as a reference to indicate that the teachings of the prior art did not enable the claims, and further, the specification provides not teaching beyond the prior art to make and use the immunoglobulin inhibitors of the instant methods.

Applicant argues on pages 24-25 that it would not be undue experimentation to determine IgA levels in normal individuals and thus determine a range for health individuals versus individuals even documenting the biological variation in health individuals. This has been considered but not found persuasive. It is apparent that the methods are not dependent on normal levels of endogenous antibodies, but on an immunoglobulin inhibitor which has not been disclosed in the art or the specification, having the specific properties of reversible inhibition by binding of a steroid hormone to a steroid hormone receptor. Thus, the instant method claims are dependent upon an immunoglobulin inhibitor with specific structural and functional properties separate from the immunoglobulin inhibitors of the prior art. However, because the structure of the immunoglobulin inhibitor has not been disclosed, one of skill in the art would not be able to assay for its presence in the background of IgA, IgG and IgM levels present in an individual. Further, the recitation of "a poly Ig receptor" and "a Fc receptor" is noted. The specification provides no guidance regarding a variant of the Fc receptor or a variant of the poly-Ig receptor which could serve to endow the binding of an Fc region with the properties of binding a reversible inhibitor of steroid responsive cell growth. Given the lack of guidance in the specification, regarding the how to make and use the immunoglobulin inhibitor, the steroid hormone receptor which causes the reversal of inhibitor after binding of said steroid hormone, "a" poly-Ig receptor or "a" Fc receptor to which the immunoglobulin inhibitor binds, one of skill in the art would be subject to undue experimentation in order make or use the instant methods.

8. Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Becchis et al (Breast Cancer Research and Treatment, 1999, Vol. 54, pp. 101-107, cited in the previous Office action) .

Becchis et al disclose that estrogen receptor positive and/or progesterone receptor negative status of breast tumors is indicative of a better prognosis of breast cancer patients (page 101, first column, lines 1-8).thus fulfills the specific embodiment of claim 20 of aiding in the prognosis of a mammalian cancer patient by detecting a population of cells expressing the estrogen receptor.

9. All other rejections and objections as set forth in Paper No. 6 are withdrawn.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.  
Patent Examiner, Group 1642

10/03/03

